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Han, Pengfei

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Increased Brain Reward Responsivity to Food-Related Odors in Obesity

Pengfei Han[1,2,3], Clemens Roitzsch[1], Annette Horstmann[4,5,6,7], Maria Pössel[5,6], and Thomas Hummel[1]

Objective: Food odors serve as powerful stimuli signaling the food quality and energy density and direct food-specific appetite and consumption. This study explored obesity-related brain activation in response to odors related to high- or low-energy-dense foods.

Methods: Seventeen participants with obesity (BMI > 30 kg/m^2; 4 males and 13 females) and twenty-one with normal weight (BMI < 25 kg/m^2; 9 males and 12 females) underwent a functional magnetic resonance imaging scan in which they received chocolate (high-energy-dense food) and cucumber (low-energy-dense food) odor stimuli. Participants' olfactory and gustatory functions were assessed by the "Sniffin' Sticks" and "Taste Strips" tests, respectively.

Results: Compared with normal-weight controls, participants with obesity had lower odor sensitivity (phenylethyl alcohol) and decreased odor discrimination ability. However, participants with obesity demonstrated greater brain activation in response to chocolate compared with cucumber odors in the bilateral inferior frontal operculum and cerebellar vermis, right ventral anterior insula extending to putamen, right middle temporal gyrus, and right supramarginal areas.

Conclusions: The present study provides preliminary evidence that obesity is associated with heightened brain activation of the reward and flavor processing areas in response to chocolate versus cucumber odors, possibly because of the higher energy density and reinforcing value of chocolate compared with cucumber.

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Study Importance

What is already known?

- Brain hyperresponsivity to external food cues is a risk for overeating and may reflect the neurobiology and pathogenesis of obesity. Food-related odors are appetitive cues representing the energy density of food; however, few studies have investigated obesity-related brain processing of high- versus low-energy-dense food odors.

What does this study add?

- Individual with obesity had decreased olfactory sensitivity. However, they demonstrated stronger brain responsivity to chocolate (high energy density) versus cucumber (low energy density) food odors in the reward-related and flavor processing–related regions, which can be framed within the incentive sensitization theory.

How might these results change the direction of research or the focus of clinical practice?

- Understanding obesity-related brain responsivity to high-calorie olfactory food cues can guide prevention and intervention efforts. Future studies should examine the food odor–related brain responses among individuals with obesity in combination with assessment of actual food choice and consumption.

Introduction

The modern obesogenic environment is characterized by the ubiquity of highly palatable and energy-dense foods with relatively low prices, leading to excessive exposure to tempting food cues (1). Sensory cues, such as the sight, smell, or taste of foods, serve as triggers to arouse food craving and memories of eating, guide subsequent food choice and consumption, and contribute to weight gain and obesity (2). People with obesity are more susceptible to external food cues (visual and olfactory) than those of normal weight (3). Obesity is related to hyperresponsivity to palatable food cues and an elevated brain activation of reward- and attention-related areas, including the striatum, orbitofrontal cortex, medial prefrontal cortex, insular cortex, anterior cingulate cortex, and hippocampus (4). Brain activation induced by food cues in these regions was shown to predict food

[1] Interdisciplinary Center on Smell and Taste, Department of Otorhinolaryngology, Technical University of Dresden, Dresden, Germany. Correspondence: Pengfei Han (p.han@foxmail.com) [2] The Key Laboratory of Cognition and Personality (Ministry of Education), Southwest University, Chongqing, China [3] Faculty of Psychology, Southwest University, Chongqing, China [4] Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland [5] IFB Adiposity Diseases, Leipzig University Medical Center, Leipzig, Germany [6] Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany [7] Leipzig University Medical Center, CRC 1052A5 'Obesity Mechanisms', Leipzig, Germany.

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choice (5), subjective food craving (5), and actual food consumption (6). The reward sensitivity to food cues may serve as a biomarker for uncontrolled eating (e.g., emotional eating) and body weight gain (7). Collectively, these findings indicate the role of altered food cue-related brain responses in the neurobiology and pathogenesis of obesity.

Most of the studies so far have used food images as stimuli, but few have used more ecological chemosensory food cues such as odor or taste. The sense of smell is tightly linked to food preference and consumption (8). Food odors have been shown to be powerful appetitive cues that provide information about the energy density and taste quality of the food through cross-channel associative learning (9). In addition, food odors can accurately reflect nutritional information such as the caloric density and main macronutrient content of food (10). For example, people can distinguish fat content of foods from odors (11) and can classify food items with the "taste" (e.g., sweet or nonsweet) or energy density (e.g., high or low energy density) (12). Food odors compared with nonfood odors were shown to activate both olfactory and reward-related brain regions, such as the piriform cortex, amygdala, orbitofrontal cortex, ventromedial prefrontal cortex, insula, ventral striatum, and anterior cingulate cortex (13-15). Until now, only a few studies have explored obesity-related neural activation to food odors. Bragulat (13) found that people with obesity compared with people with normal weight had greater activation of the bilateral hippocampus and parahippocampal area in response to preferred food odors versus nonfood odors. However, another study showed no effect from obesity on brain responses to palatable food odors versus nonfood odors (14).

The current study aimed to investigate obesity-related brain responses to food odors, especially when considering relative salience of odor-related foods (e.g., high-calorie food vs. low-calorie food). We hypothesized that individuals with obesity versus individuals with normal weight would have stronger reward brain activation in response to high-calorie- versus low-calorie-food-related odors (hypothetical regions including striatum, orbitofrontal cortex, insula, and thalamus). It has been established that excessive body weight was related to impaired olfactory functions, including reduced odor discrimination ability or odor sensitivity (16). The current study measured the olfactory functions of the participants using the "Sniffin' Sticks" test in order to explore whether altered brain responses to food odors are associated with the impaired olfactory function.

Methods

Participants

Seventeen participants with obesity (BMI > 30 kg/m^2; 4 males and 13 females) and twenty-one control participants with normal weight (BMI < 25 kg/m^2; 9 males and 12 females) were included in the study (Table 1). All participants were right-handed and nonsmoking and were interviewed for a thorough history about their medication use. None of the participants reported anything about medication use that may interfere with olfactory function or in relation to psychiatric disorders. Participants were free of nasal pathology (e.g., polyps or other forms of rhinosinusitis) as screened by a physical otorhinolaryngological examination including nasal endoscopy. Other exclusion criteria included claustrophobia, pregnancy, and metallic implants. Two participants of the normal-weight group had arterial hypertension (one with Hashimoto). In the group with obesity, four had arterial hypertension (one with diabetes), two had hypothyroidism, and another one had both diabetes and Hashimoto. Participants provided written informed consent prior to the experiment and received a modest monetary reward for participation. The study design was in accordance with the Declaration of Helsinki and had been approved by the Ethics Committee of the Medical Faculty Carl Gustav Carus at the Technical University of Dresden.

Olfactory and gustatory function test

Olfactory function was assessed using the Sniffin' Sticks test (Burghart GmbH, Wedel, Germany) (17). The kit comprised three subtests: odor threshold test for phenylethyl alcohol (single staircase, three-alternative forced choice task), odor discrimination test (16 triplets of odors, three-alternative forced choice task), and odor identification test (16 common odorants, multiple forced choice from four verbal descriptors per odor). The composite odor threshold, discrimination, and identification (TDI) score ranged from 1 to 48 points.

Gustatory function was assessed by means of the "Taste Strips" test (18). Twenty taste-impregnated filter-paper strips were presented in a randomized order regarding taste qualities in increasing concentrations, as a whole-mouth procedure in the middle of the anterior portion of the tongue. Participants were asked to identify the taste quality by choosing one of four possible answers (sweet, sour, salty, and bitter). Before assessment of each strip, the mouth was rinsed with water. The gustatory function test score was the number of correctly identified strips with a range from 0 to 16. The following concentrations were used for impregnation of the strips: sweet: 0.4, 0.2, 0.1, and 0.05 g/mL of sucrose; sour: 0.3, 0.165, 0.09, and 0.05 g/mL of citric acid; salty: 0.25, 0.1, 0.04, and 0.016 g/mL of sodium chloride; and bitter: 0.006, 0.0024, 0.0009, and 0.0004 g/mL of quinine hydrochloride.

Odor stimuli

Chocolate and cucumber odors (Fragrance Resources, Hamburg, Germany) were selected as food stimuli. A block design was adopted

TABLE 1 Demographics for NW and OB groups

	NW (n = 21)	OB (n = 17)	Comparisons
Age (mean ± SD)	36.2 ± 10.1	37.4 ± 9.9	$F(1,36) = 0.12$; $P = 0.74$
BMI (mean ± SD)	21.8 ± 2.1	38.2 ± 4.5	$F(1,36) = 224.6$; $P < 0.001$
Sex (M/F)	9/12	4/13	$\chi^2 = 1.56$; $P = 0.31$
Age range (y)	23-56	19-54	
BMI range	18.96-24.49	32.04-45.73	

F, female; M, male; NW, normal weight; OB, obesity.

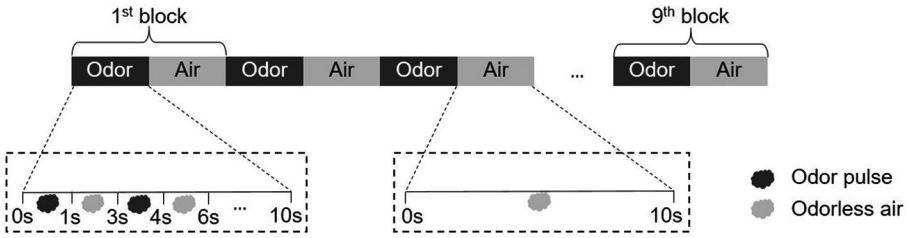

Figure 1 Schematic representation of the experimental blocks design protocol used during the fMRI sessions. One out of two similar sessions is displayed.

for odor stimulation. Nine 20-second blocks were set up for each odor condition. Each block started with a 10-second "odor period" in which odorized air was delivered to the participants' nostrils, followed by a 10-second "baseline period." To minimize odor habituation, the chocolate and cucumber odors were presented intermittently during the odor period, with 1-second odorized air and 2-second odorless air. During the baseline period, only odorless air was presented (Figure 1). This approach permitted an independent assessment of the odor-baseline response for each individual odor stimuli. Odorized and odorless air was delivered at a flow of 2 L/min using a portable olfactometer (19). The order of odor administration was fixed (chocolate in the first run and cucumber in the second run). Before the scan, participants were trained to use the velopharyngeal closure technique (breathing only through the mouth by lifting the soft palate). This technique enables olfactory stimulation to be unaffected by patterns of inhalation and exhalation. All participants refrained from consuming food or drinks (except water) for 2 hours before the experiment. Participants were not aware of the quality of the odors (e.g., the odor-related food sources) to minimize the effect of individual differences in odor preference on brain activation.

Imaging data acquisition and preprocessing

Data were acquired on a 3-T scanner (Siemens Sonata, Erlangen, Germany) using an eight-channel head coil. Functional images were collected per individual using a T2-weighted echo-planar imaging sequence (repetition time [TR] = 2,500 milliseconds; echo time [TE] = 30 milliseconds; flip angle = 90°; voxel size = 3×3x3.75 mm^3; field of view = 192 × 192 mm). In addition, a high-resolution T1-weighted anatomical image was acquired using a standard magnetization prepared rapid acquisition gradient echo sequence (TR = 2,530 milliseconds; TE = 2.34 milliseconds; field of view = 256 × 256 mm; voxel size = 1×1×1 mm^3).

Magnetic resonance imaging (MRI) data for each participant were preprocessed using SPM12 (Statistical Parametric Mapping; Welcome Department of Cognitive Neurology, London, UK) in MATLAB (version 2013a; MathWorks, Natick, Massachusetts) as follows, with the default settings unless reported otherwise. First, the functional images from each run were realigned to the first image of the first functional run and unwrapped. Second, the anatomical image was coregistered to the averaged mean image from the realignment procedure. Third, the coregistered anatomical images were segmented, and the functional images were spatially normalized to the Montreal Neurological Institute (MNI) space with a voxel size of 2×2×2 mm^3 using the deformation field estimated during the segmentation process. Fourth, the spatially normalized echo-planar images were smoothed using a Gaussian kernel of 8-mm full-width at half maximum. Finally, removal of head motion artifacts using ArtRepair (version 4; Stanford University, Stanford, California) was applied to the preprocessed images based on the following rules: image-to-image motion less than 0.5 mm/TR and total number of images repaired less than 20%. Of 38 participants, images from 4 participants were repaired using the default threshold in ArtRepair; none was excluded.

Functional MRI data analysis

The entire odor and baseline block was modeled and calculated for mean blood oxygen level–dependent signal changes. For the individual level, the baseline period was first subtracted from the respective odor period, resulting in contrasts of interest corresponding to each odor condition (chocolate: con_0001 or cucumber: con_0002) and the collapsed odor condition (chocolate + cucumber: con_0003). On the group level, brain activation to collapsed odors and for each type of odor was analyzed using one-sample *t* test. The brain response difference between two odors was analyzed using paired *t* test. To assess the interaction of obesity status and food odor type on brain activation, a 2 × 2 flexible factorial model was set with the factor participant, participant group (normal weight, obesity), and odor type (high calorie and low calorie). In addition, because there are well-known sex differences in the response to food-related stimuli, we set an independent two-sample *t* test to examine sex differences of brain activation to collapsed food odor and with a 2 × 2 flexible factorial model for interaction between sex and odor type. Results for these tests were included as supporting information.

Statistical analysis was conducted on a whole-brain level. The brain response to collapsed odor among all participants was set at $P < 0.05$ familywise corrected with a cluster extent (k) of five voxels. To control for multiple statistical testing within the entire brain, we maintained a cluster-level false positive detection rate at $P < 0.05$ using an initial voxel-level threshold of $P < 0.005$ with a cluster extent (k) empirically determined by Monte Carlo simulations (n = 5,000 iterations), by means of AlphaSim procedure (20). This was done using the REST toolbox (http://www.restfmri.net/forum/REST_V1.7) (21). The minimum cluster size was determined for each group-level test separately to achieve a corrected clusterwise probability of $P < 0.05$ across the whole brain. Mean response signals of the significant cluster were extracted using Marsbar toolbox (http://marsbar.sourceforge.net/) and plotted using Prism 6 (GraphPad Software, San Diego, California). Significant brain regions were labeled and reported with the help of Automated Anatomical Labeling 3 (AAL3) toolbox (http://www.gin.cnrs.fr/tools/aal-aal3).

Non-functional MRI statistical analysis

Data were analyzed using SPSS Statistics version 23.0 for Windows (IBM Corp., Armonk, New York). Group differences for BMI, age, gender, and chemosensory testing scores (Sniffin' Sticks and Taste

Strips tests) were assessed via ANOVA or Pearson χ^2 tests, with $\alpha = 0.05$.

Results

Participants' demographics

No significant differences were observed between the normal-weight group and the group with obesity regarding age or sex (Table 1). BMI was significantly higher for the group with obesity as compared with the normal-weight group (Table 1).

Olfactory and gustatory function

Compared with the normal-weight group, the group with obesity demonstrated significantly lower odor sensitivity ($F(1,34) = 4.54$; $P = 0.04$), and a trend toward lower odor discrimination performance ($F(1,34) = 3.60$; $P = 0.07$). Participants with obesity showed reduced overall olfactory function (combined TDI) compared with normal-weight participants ($F(1,34) = 7.06$; $P = 0.01$). There was no difference regarding odor identification. Participants with obesity had normal gustatory function as measured by the Taste Strips test (Table 2).

Brain responses to food odors

Among the whole study sample ($N = 38$), we observed activation of the right ventral anterior insula, right inferior frontal operculum, right putamen, and left middle insula in response to collapsed odor stimulation (Table 3). For individual odors, the chocolate odor induced activation of the right putamen, left middle insula, and the right precentral and postcentral gyrus. No significant activation was found for cucumber odor stimulation (Table 3).

For all participants, the chocolate compared with cucumber odor activated the bilateral Rolandic operculum, right putamen, right insula, and left postcentral gyrus. The cucumber odor activated the left angular gyrus compared with chocolate odor (Table 4). In the normal-weight group, chocolate versus cucumber odor showed superior activation in the right Rolandic operculum, whereas stronger activation was observed in the right supramarginal, right angular gyrus, and left middle temporal gyrus in response to cucumber versus chocolate odors. For participants with obesity, the chocolate odor recruited stronger activation of the right middle insula extending to putamen, the right inferior frontal operculum, right supramarginal, and left dorsal anterior insula. No superior activation was found in response to cucumber compared with chocolate odors (Table 4).

Brain activation between normal-weight group and group with obesity

Compared with the group with obesity, the normal-weight group showed enhanced right middle insular activation to collapsed food odors (chocolate and cucumber). However, a significant group × odor type interaction was observed. Brain activation in response to chocolate

TABLE 2 Olfactory and gustatory functions for NW and OB groups

	NW (n = 21)	OB (n = 17)	Comparisons
Odor threshold (mean ± SD)	8.5 ± 2.0	6.8 ± 2.4	$F(1,34) = 4.54$; $P = 0.04$
Odor discrimination (mean ± SD)	12.7 ± 2.1	11.4 ± 2.5	$F(1,34) = 3.60$; $P = 0.07$
Odor identification (mean ± SD)	13.8 ± 1.2	13.2 ± 2.4	$F(1,34) = 0.80$; $P = 0.38$
TDI score (mean ± SD)	35.1 ± 2.9	31.3 ± 4.9	$F(1,34) = 7.06$; $P = 0.012$
Taste Strips (mean ± SD)	12.1 ± 2.1	12.4 ± 1.7	$F(1,33) = 0.40$; $P = 0.53$

Taste Strips test measure the overall gustatory function including sweet, sour, bitter and salty tastes.
NW, normal weight; OB, obesity; TDI scores, the sum of results obtained for odor threshold, odor discrimination, and odor identification measures.

TABLE 3 Brain response (pFWEcorr. < 0.05 and cluster size > 5 voxels across the whole brain) to odor stimuli among all participants (N = 38)

	k	Peak T	x,y,z			Region (AAL)
Collapsed odors	16	7.20	36	10	–10	Ventral anterior insula R
	8	6.60	38	16	12	Inferior frontal operculum R
	6	6.06	36	–2	6	Putamen R
	6	5.78	–36	–6	8	Middle insula L
Chocolate odor	21	6.65	32	8	–10	Putamen R
	18	6.46	–36	–4	2	Middle insula L
	8	6.22	56	4	20	Precentral gyrus R
	20	6.17	56	–12	22	Postcentral gyrus R
Cucumber odor	-	-	-	-	-	-

AAL, Automated Anatomical Labeling; L, left hemisphere; pFWEcorr., P value with familywise error corrected; R, right hemisphere.

TABLE 4 Brain response between two odors in NW and OB groups

	k	Peak T	x,y,z			Region (AAL)
Chocolate > cucumber all	837	5.15	56	–20	22	Rolandic operculum R
	77	4.20	30	12	–10	Putamen R
	386	3.87	–32	–4	4	Rolandic operculum L
	75	3.76	28	14	4	Putamen R
	77	3.76	–60	–20	14	Postcentral gyrus L
	71	3.73	40	–4	10	Insula R
	97	3.66	–60	–16	30	Postcentral gyrus L
Cucumber > chocolate all	69	3.38	–46	–54	26	Angular gyrus L
Chocolate > cucumber NW	394	4.41	64	–16	12	Rolandic operculum R
Cucumber > chocolate NW	90	4.49	68	–42	28	Supramarginal R
	100	3.96	52	–56	34	Angular gyrus R
	40	3.76	–58	–40	6	Middle temporal gyrus L
Chocolate > cucumber OB	172	6.33	32	8	–10	Middle insula/putamen R
	229	4.91	52	12	16	Inferior frontal operculum R
	287	4.70	56	–20	22	Supramarginal R
	180	4.44	–44	10	6	Dorsal anterior insula L
Cucumber > chocolate OB	-	-	-	-	-	-

Whole-brain analyses with $P < 0.005$ and cluster size $k > 67$ voxels for all participants; $k > 34$ voxels for NW group; $k > 65$ voxels for OB group.
AAL, Automated Anatomical Labeling; L, left hemisphere; NW, normal weight; OB, obesity, R, right hemisphere.

TABLE 5 Significant brain activation to HCO and LCO between NW and OB groups

	k	Peak T	x,y,z			Region (AAL)
NW > OB [HCO/LCO]	55	4.09	48	–4	–8	Middle insula R
OB > NW [HCO/LCO]	85	4.85	22	20	28	White matter
OB [HCO > LCO] > NW [HCO > LCO]	61	4.03	40	–38	2	Middle temporal gyrus R
	125	3.97	–52	16	0	Inferior frontal operculum L
	80	3.90	0	–54	–14	Vermis L R
	114	3.65	–58	–40	6	Middle temporal gyrus L
	50	3.58	32	4	–12	Putamen/ventral anterior insula R
	115	3.44	56	–42	32	Supramarginal R
	96	3.38	52	12	16	Inferior frontal operculum R

All reported results were significant at uncorrected $P < 0.005$ and cluster size of $k > 52$ (two-sample t test) $k > 38$ (flexible factorial model test) contiguous voxels across the whole brain.
AAL, Automated Anatomical Labeling; HCO, high-calorie chocolate odor; L, left hemisphere; LCO, low-calorie cucumber odor; NW, normal weight; OB, obesity, R, right hemisphere.

versus cucumber odors was significantly stronger among individuals with obesity compared with individuals with normal weight. Activated regions included the bilateral inferior frontal operculum, left superior temporal cortex, right cerebellar vermis, left middle temporal gyrus, right ventral anterior insula extending to putamen, and right supramarginal areas (Table 5 and Figure 2). When the same analyses were performed with the TDI score included as a covariate of no interest, results remained significant. There was no significant superior brain activation in the group with obesity compared with the normal-weight group in response to cucumber versus chocolate odors.

Discussion

The current study demonstrated stronger brain activation in response to chocolate versus cucumber odors in the group with obesity compared with the normal-weight group. Only a handful of studies in the literature have looked at obesity-related brain responses to food odors. Bragulat et al. (13) showed obesity-related greater activation in the hippocampus and parahippocampal gyrus in response to preferred food odors versus nonappetitive nonfood odors. However, another study found no effect of obesity on brain responses to palatable food versus nonfood odors (14). The current study found multiple brain regions with heightened activation to chocolate in contrast to cucumber odors among individuals with obesity as compared with individuals with normal weight. The frontal operculum is part of the brain network for food flavor processing and a suggestive area responding to multimodal integration, as well as unimodal olfactory and gustatory stimuli (22). Adolescents with obesity showed greater brain responses of the frontal operculum to food reward anticipation as compared with lean adolescents (23,24). In a recent study, people with obesity relative to those with normal weight demonstrated enhanced activation of the inferior frontal operculum

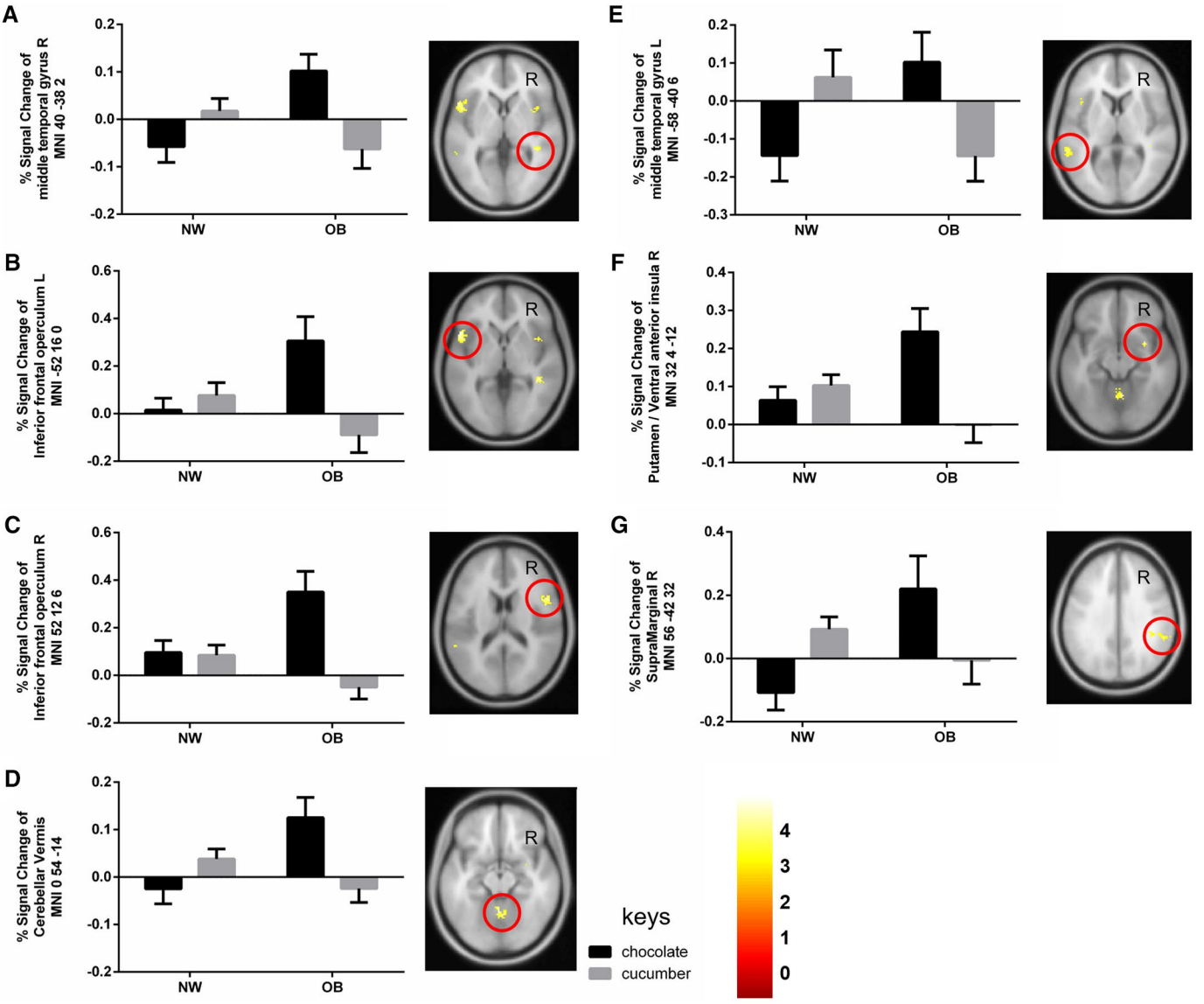

Figure 2 Stronger brain activation of the group with obesity versus the normal-weight group in response to chocolate > cucumber odorous stimuli. (A) Left superior temporal cortex; (B) right cerebellar vermis; (C) left inferior temporal operculum; (D) left middle temporal gyrus; (E) right Rolandic operculum; (F) right putamen/insula; (G) right inferior parietal lobule. Brain maps thresholded at $P \leq 0.005$ and $k \geq 38$ voxels and displayed on a template provided in SPM (\spm12\canonical\avg152T1.nii,1). MNI, Montreal Neurological Institute; NW, normal weight; OB, obesity. [Color figure can be viewed at wileyonlinelibrary.com]

during a food portion choice task under a pleasure mind-set (e.g., explicitly shift attentional focus to food pleasure) and that the activation was correlated with increased portion size selection (25). Moreover, the activation was also found in a cluster of the ventral anterior insula extending to putamen. These regions have been well documented as key areas involved in food reward processing of food odors and flavors (26) and have been shown with increased activation among people with obesity during high-calorie versus low-calorie visual food cue processing (27,28). Meta-analytical research found that the anterior insula/frontal operculum is consistently activated by modality-independent reward (food, erotic, or monetary), with the ventral anterior insula more recruited by food-related reward (29).

Individuals with obesity compared with normal-weight controls also demonstrated increased activation of the cerebellar vermis in response to chocolate versus cucumber odors. The vermis has been suggested to play a role in bottom-up controlling of feeding behavior, particularly in driving motivation for appetitive foods (30,31). The recruitment of vermis activation was also found in relation to self-reported uncontrolled eating, which comprises multifaceted eating characteristics including hedonic hunger, food craving, or emotional eating (7). In human functional MRI (fMRI) studies, enhanced vermis activation was shown in normal-weight individuals in response to images depicting high- versus low-calorie foods (32). Moreover, participants with obesity compared with participants with normal weight showed stronger cerebellar activation in response to food versus nonfood cues (33). Thus, the current result has extended the literature by showing the obesity-related alteration of cerebellar responses to odors associated with high-calorie food. In addition, increased activation of the middle temporal gyrus has been shown during processing of appetitive or high-calorie food cues

(32,34). Although less reported, the supramarginal area was shown to be involved in processing of unhealthy food cues (35). Taken together, the elevated brain responsivity to chocolate versus cucumber odors in individuals with obesity may support a reward hyperresponsivity to high- versus low-energy-dense food cues and this is in accordance with a previous study showing obesity-related heightened activation in response to high-calorie food pictures (28). The food cue–elicited neural hyperresponsivity among individuals with obesity can be best framed within the incentive sensitization theory (4).

Obesity-related impairment of olfactory functions has been reported previously. A recent meta-analysis suggested a moderate decreased olfactory function among individuals with obesity, which was mainly due to impaired odor discrimination ability and a trend of declining odor sensitivity (16). Results from the current study showed decreased olfactory sensitivity (to a nonfood odor 2-phenylethanol) and overall Sniffin' Sticks TDI scores in the group with obesity compared with the normal-weight group. However, one study found an increased sensitivity to chocolate odor among people with obesity (36), suggesting a possible discrepancy regarding sensitivity to food- or nonfood-related odors in obesity. Moreover, the brain activation of the group × odor type interaction was not affected when including odor threshold as a covariate, implying that the impaired olfactory function was not the inherent cause for this effect. A recent study suggested a link between insulin resistance and reduced olfactory sensitivity (37). Whether obesity-related alteration of olfaction is also generalized to all types of food odors remains to be elucidated.

Several limitations of the study need to be noted. First, several participants with diabetes or thyroid dysfunction were not excluded from the analyses because of sample size issues. Second, only two odors were tested, which makes the generalization of the results difficult. With a nonfood odor, it would allow a better separation of food and energy factors. Besides, subjective evaluation of tested odors, such as the intensity, valence, odor-related taste quality, healthiness, or preference, would have eliminated the possibility that differences in brain responses were driven by variations in these aspects rather than by the energy density. Third, although the cluster-extent threshold can increase the sensitivity of the test, it may bring false-positive results. Additionally, we did not control for the menstrual cycle of female participants, as it has previously been shown that olfactory perception (38) or food-related neural processing (39,40) is influenced by the menstrual cycle and related sex hormone levels (e.g., testosterone and estradiol) in women. The hormonal changes related to oral contraceptive intake were another potential variable affecting the result (40). Besides, although the use of velopharyngeal closure can assure that sniffing is not related to the odor delivery, there are some findings in the literature suggesting that it may alter the nature of orbitofrontal activation (41). Respiration-triggered event-related fMRI designs may yield a stronger activation of the olfactory cortex compared with fixed-timing odor delivery (42). Nevertheless, we chose a less complex experimental design with fixed-timing odor delivery, which was previously validated in our lab. Still, the whole duration of odor stimulation was relatively short (nine odor blocks in a total of 90 seconds). Therefore, findings from the current study should be used for hypothesis generation and not confirmatory inference. Future studies including larger sample sizes and a more elaborate design are warranted.

There are relevant questions that remain open. First, orthonasal food odor (as in this study) signals availability, whereas retronasal food odor usually refers to the mouth. Orthonasal versus retronasal odor stimuli have shown different brain activations (43). Whether obesity-related neural processing of orthonasal versus retronasal food odors differ is unclear. Second, the passive odor perception paradigm has limitations in probing specific aspects of eating-related food cue processing; it would be interesting for future studies to apply specific tasks (or instructions) during olfactory fMRI. Additionally, a food intake setup could probe the question of whether heightened brain responses to high- versus low-calorie food odors predict actual food choice and consumption. Third, although subjective hunger and satiety ratings seem to have minimal to no influence on food cue-related brain responses in obesity (44), other studies have shown that odor perception is largely dependent on hunger status (45), and therefore future studies would benefit from testing odor-induced brain responses in obesity at hunger and satiated status.

In conclusion, our preliminary findings suggested that although individuals with obesity had reduced olfactory function, compared with those with normal weight, they demonstrated an elevated activation of the reward and flavor processing brain areas when exposed to an odor strongly associated with sweet caloric food (chocolate) in contrast with a low-caloric food odor (cucumber).O

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Supporting information: Additional Supporting Information may be found in the online version of this article.

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